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# Successful re-introduction of lamotrigine after initial rash

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The aim of this study was to determine whether lamotrigine can be re-introduced safely and with a benefit in young people who previously had a mild rash associated with the first introduction of this drug. In the first 150 young people (5–19 years old) treated with lamotrigine in a special centre for epilepsy, seven developed a mild rash soon after starting the drug. In none of these cases was the rash severe, nor was there any mucous membrane involvement. The lamotrigine was stopped immediately when the rash was identified and was subsequently re-introduced, using a special very-low-dose-escalation regime, starting with 0.1 mg/day total daily dose, after periods ranging from 47 to 236 days. It was possible to re-introduce the lamotrigine without recurrence of persistent rash and without any adverse effects in all seven cases. The re-introduction of lamotrigine was associated with improvement in five of the seven cases. It is recommended that lamotrigine is stopped as soon as any rash attributable to the drug develops but it may be possible to re-introduce the drug after mild rash using a very-slow-dose-escalation regime, with a benefit in at least some cases.



*Key words:* lamotrigine; rash; re-introduction; slow; escalation.

## INTRODUCTION

Skin rash is one of the commonest adverse effects of lamotrigine. Messenheimer[1] has recently carried out a comprehensive review of this subject. The incidence appears to relate closely to dose escalation; for example, within a single study, the rash rate varied from 5% to 39%, depending on dose escalation[2]. Rash is more likely to occur if the patient is already taking sodium valproate, which prolongs the half-life of lamotrigine[3]. Serious reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis have been reported and fatalities have occurred[4,5].

## PATIENTS AND METHODS

In the first 150 children and teenagers (age range 5–19 years) treated at a special epilepsy centre, seven developed a mild rash. There was no history of rash with previous antiepileptic medication. Mild in this context was defined as including none of the following: mucous membrane involvement, blisters/bullae or extensive desquamation. The term mild also implied that there was no fever, lymphadenopathy or systemic involvement attributable to the drug. In every case the lamotrigine was discontinued immediately but was re-introduced, using a special very-slow-dose-escalation regime, commencing with 0.1 mg/day total daily dose (see Table 1). Eames[6] had suggested that such a regime might be used to prevent rash developing with carbamazepine. The lamotrigine was re-introduced because seizure control was unsatisfactory with other available drugs. In some cases there had been an apparent good initial response to lamotrigine but in other cases the drug had not been given for long enough to allow any assessment to be made. The lamotrigine was re-introduced after a minimum period of 6 weeks (47–236 days) from the time when the drug was initially stopped. The minimum of 6 weeks was chosen to allow plenty of time for any initial reaction to subside completely.

The low doses were achieved by breaking the scored 5 mg dispersible tablet into quarters and dispersing a quarter tablet into 12.5 ml of water. 1 ml of this liquid was equivalent to 0.1 mg of lamotrigine. Before the dispersible tablets became available, the smaller doses were obtained by grinding a 25 mg tablet; the powder obtained was carefully homogenized into lactose powder which was weighed to give the appropriate doses. The powder was placed into standard gelatine capsules giving the appropriate dose at each stage.

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Table 1: Very-low-dose-escalation re-introduction regime for lamotrigine.

| | |
|---|---|
| Week 1 | 0.1 mg daily[a] |
| Week 2 | 0.1 mg bd |
| Week 3 | 0.2 mg bd |
| Week 4 and 5 | 1 mg daily |
| Week 6 and 7 | 2 mg daily |
| Week 8 | 4 mg daily |
| Week 9 and 10 | 6.25 mg daily |
| Week 11 and 12 | 12.5 mg daily |

After week 12 the dose was doubled at intervals of no less than 2 weeks until a dose of 50 mg was reached. No subsequent dose in increments exceeded 50 mg and the increases were carried out no more frequently than at fortnightly intervals.
[a] Note: 0.1 mg is the *total* daily dose: not to be confused with the 0.1 mg/kg daily used as a standard introduction for patients taking valproate at Lingfield—see text.

## RESULTS

These are shown in Table 2.

## DISCUSSION

The development of rash with lamotrigine has been linked to the initial dose and the rate of dose-escalation. This was clearly shown in the study of lamotrigine in the prophylaxis of migraine[2]. In that study, a fixed dose regime of 200 mg a day resulted in the withdrawal of lamotrigine because of rash in 7 of 18 patients (39%) whereas the group in which the lamotrigine was escalated more slowly, beginning with 25 mg per day and increasing at two-week intervals to 50 mg daily and then 200 mg daily resulted in a withdrawal rate of 1 in 19 (5%), which was similar to placebo. A number of the cases reported here were prescribed lamotrigine before the current UK dosing regimes (see Table 3a and b), were recommended. The dose regimes used for cases 1, 2, 3 and 7 were not within these recommendations but the dosages for cases 4, 5 and 6 were. This raises the question of whether these recommendations are appropriate. The regime adopted at St Piers Lingfield over recent years is more conservative and simpler. The dose is commenced at 1 mg/kg/day for those not taking sodium valproate and 0.1 mg/kg/day for those who are taking sodium valproate. The dose is doubled at two-weekly intervals but in no case does any dose increment exceed 50 mg. Since this regime was introduced, only one mild rash has been seen in over 100 cases. It should be noted that the current UK guidelines are due for revision and that the US guidelines have recently been revised. The current US guidelines are close to the practice adopted at Lingfield in recent years (see Table 3c and d).

Were all the rashes in this series clearly related to the lamotrigine? The timing of the rash is strongly presumptive evidence in most cases, although there was possibly some doubt about case 2, because he had developed a rash at other times, and in case 5 because he had signs of an upper respiratory tract infection and was treated with amoxycillin which is known to be associated with a similar type of rash. The evidence for the rash being related to the lamotrigine is stronger in case 4 because a mild rash recurred when the lamotrigine was recommenced.

The very-slow-introduction regime was based on previous work with carbamazepine. Eames[6] reported on seven cases of rash with carbamazepine managed by 'desensitization'. The dose-escalation regime he used was based on a single case-report by Smith and Newton[7]. Chadwick *et al.*[8] had also linked the speed of dose escalation with incidence of rash associated with carbamazepine. The regime used in our study closely follows that of Eames for carbamazepine. Whether this regime represents a true 'desensitization' or not remains open to debate. Those using this regime for carbamazepine have adopted a policy of continuing the drug if a very mild rash occurs during the 'desensitization' period. The dose may be held at the same level if a mild rash occurs and if, in the opinion of the clinician, there are no other untoward signs such as systemic illness, suggesting that the drug should be stopped. The approach taken is that a mild rash at such a low dose is unlikely to develop into a serious rash. Although limited experience using this regime has not led to any serious rashes, it cannot be concluded that serious rashes could never occur in such circumstances. Re-introduction should only be undertaken if close medical supervision can be offered so that if a patient were to develop any symptoms causing concern, immediate action could be taken.

Is it necessary to use such a slow re-introduction regime? Schlumberger *et al.*[3] described the successful re-introduction of lamotrigine in four out of five patients after sodium valproate was stopped. However, the re-introduction regime was not stated. Tavernor *et al.*[9] described seven patients, four of whom were children or teenagers, in whom lamotrigine was re-introduced after initial rash. A further patient, an 8-year-old child, developed a rash after taking lamotrigine for 7 months but the lamotrigine was not stopped completely before being increased again, implying that this was not, strictly speaking, re-introduction of the drug. In two of these cases the dose was built over a period of at least 6 months, representing a slower overall dose escalation rate but the lamotrigine was recommenced at much higher starting doses: 12.5 mg daily or on alternate days. In one of these cases the rash recurred when the drug was recommenced at 12.5 mg on alternate days but it was possible to re-introduce lamotrigine again, using an even slower escalation regime: 0.5 mg on alternate days, slowly building up

Table 2: Summary of seven cases of rash associated with lamotrigine.

| No. | Age | Sex | Vpa comed | Other comed | Start dose mg/day | Dose weeks 3–4 mg/day | Start dose (mg/kg/day) | Dose weeks 3–4 mg/kg/day | Dose > recom (UK) | Dose > recom (US) | Rash on day number | Fever | Lymph-adeno-pathy | Other cause likely | Re-started after (days) | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 14 | M | No | Cbz | 100 | 150 | 1.8 | 4.4 | Yes | Yes | 24 | No | No | No | 236 | Seizure-free |
| 2 | 6 | M | No | Pb | 50 | 100[a] | 2 | 4.2[a] | Yes | Yes | 13 | No | No | Possible[b] | 47 | Seizure-free |
| 3 | 15 | M | Yes | Cbz | 12.5 | 25 | 0.3 | 0.6 | Yes | Yes | 57 | No | No | No | 76 | Nonconvulsive status epilepticus episodes abated |
| 4 | 14 | M | No | Cbz | 25 | 50 | 0.6 | 1.2 | No | No | 26 | Yes[c] | No | No[c] | 52 | Seizure not controlled. Lamotrigine discontinued |
| 5 | 18 | M | No | Esm, Vgb, Cbz | 50 | (stopped on day 13) | 1.1 | — | No | Yes | 13 | No[d] | Yes[d] | Possible amoxycillin[d] | 92 | Seizures improved but continued |
| 6 | 16 | M | Yes | Cbz | 5 | (stopped on day 3) | 0.1 | — | No | No | 3 | No | No | No | 47 | No benefit |
| 7 | 11 | M | Yes | — | 12.5 | 25 | 0.4 | 0.7 | Yes | Yes | 21 | No | No | No | 161 | Absence seizures fully controlled |

[a] Increase actually on day 13. Rash appeared that day and lamotrigine then stopped.
[b] Had previously had occasional rashes with no apparent cause.
[c] Associated with inflamed pharynx, mildly inflamed tympanic membrane and green nasal discharge.
Because he also developed a very mild rash 22 days after re-introduction, the initial rash was considered to be attributable to the lamotrigine. Because the dose at that stage of the re-introduction was still very low (0.4 mg daily total dose) and the rash very mild, the drug was continued and the rash resolved.
[d] Ten days previously he had been febrile with lymphadenopathy and an inflamed right tympanic membrane. Amoxycillin was prescribed.
Comed = comedication,
Vpa = sodium valproate, Cbz = carbamazepine, Pb= phenobarbital, Esm = ethosuximide, Vgb = vigabatrin
Dose > recom = dose exceeds recommended schedule.

Table 3a: Current UK lamotrigine dose-escalation schedule for children aged 2–12 years on combined drug therapy.

| Concurrent AED | Weeks 1–2 | Weeks 3–4 | Maintenance dose |
|---|---|---|---|
| VPA | 0.2 mg/kg/day (once daily) | 0.5 mg/kg/day (once daily) | 1–5 mg/kg/day (once daily or in two divided doses) increasing every 1–2 weeks by 1 mg/kg/day increments |
| EIAEDs[a] | 2 mg/kg/day (in two divided doses) | 5 mg/kg/day (in two divided doses) | 5–15 mg/kg/day (in two divided doses) increasing by 2–3 mg/kg every 1–2 weeks) |

[a] EIAED = enzyme-inducing antiepileptic drugs such as phenytoin, phenobarbital and carbamazepine. Patients who are taking both valproate (VPA) and an EIAED should be dosed according to the co-administration with VPA guidelines.

to 12.5 mg over 6 months, with no recurrence of the rash. It could be argued that 6 months is unnecessarily long. The most important period appears to be the first 6–8 weeks of treatment, since most rashes occur over this time. Whether the very-low-dose-escalation regime used over the first 6–8 weeks followed by a more rapid escalation would be equally tolerated remains unclear.

Would the incidence of the serious reactions reported in a number of papers[4, 5, 10, 11] be reduced by a slower dose escalation? In a recent publication, factors associated with serious rash in children taking lamotrigine were examined, using available data from clinical trials[12]. A higher initial dose or more rapid dose escalation than currently recommended were identified as associated factors in 8 of the 10 cases. The weight of evidence suggests that starting dose and dose-escalation rates should be kept well within the pharmaceutical company guidelines[13]. It will be of great interest to discover whether the more conservative regime already recommended in the US will lead to a lower rate of both serious and mild rashes.

Table 3b: Current UK lamotrigine dose-escalation schedule for adults and children over 12 years on combined drug therapy.

| Concurrent AED | Weeks 1–2 | Weeks 3–4 | Maintenance dose |
|---|---|---|---|
| VPA | 12.5 mg (given as 25 mg onalternative days) | 25 mg once daily | 100–200 mg (once daily or in two divided doses) increasing by 25–50 mg every 1–2 weeks) |
| EIAEDs[a] | 50 mg (daily) | 100 mg (in two divided doses) | 200–400 mg (in two divided doses increasing by 100 mg every 1–2 weeks) |

[a] EIAED = enzyme-inducing antiepileptic drugs such as phenytoin, phenobarbital and carbamazepine. Patients who are taking both valproate (VPA) and an EIAED should be dosed according to the co-administration with VPA guidelines.

Table 3c: Current US lamotrigine dose-escalation schedule for children 2–12 years. (Based on package insert 1998).

| Concurrent AED | Weeks 1–2 | Weeks 3–4 | Maintenance dose |
|---|---|---|---|
| VPA | 0.15 mg/kg/day once daily or in two divided doses | 0.3 mg/kg/day once daily or in two divided doses | 1–5 mg/kg/day increasing every 1–2 weeks by up to 0.3 mg/kg/day increments |
| EIAEDs[a] | 0.6 mg/kg/day once daily or in two divided doses | 1.2 mg/kg/day once daily or in two divided doses | 5–15 mg/kg/day increasing every 1–2 weeks by up to 1.2 mg/kg/day increments |

[a] EIAED = enzyme-inducing antiepileptic drugs such as phenytoin, phenobarbital and carbamazepine. Patients who are taking both valproate (VPA) and an EIAED should be dosed according to the co-administration with VPA guidelines.

Table 3d: Current US lamotrigine dose-escalation schedule for adults and children over 12 years.

| Concurrent AED | Weeks 1–2 | Weeks 3–4 | Maintenance dose |
|---|---|---|---|
| VPA | 25 mg every other day | 25 mg daily | 100–400 mg daily or in two divided doses increasing by 25–50 mg/day every 1–2 weeks. Usual maintenance dose in patients adding lamotrigine to VPA alone ranges from 100–200 mg/day. |
| EIAEDs[a] | 50 mg daily | 100 mg daily in two divided doses | 300–500 mg daily in two divided doses increasing by 100 mg/day every 1–2 weeks |

[a] EIAED = enzyme-inducing antiepileptic drugs such as phenytoin, phenobarbital and carbamazepine. Patients who are taking both valproate (VPA) and an EIAED should be dosed according to the co-administration with VPA guidelines.

## CONCLUSIONS AND RECOMMENDATIONS

Lamotrigine was successfully re-introduced in seven children and teenagers who developed rash when the drug was initially prescribed. Five of these seven young people appeared to benefit from the drug. When using any drug, the risk/benefit ratio must be considered. Although avoiding the initial rash by using low starting doses and escalation rates would be the preferred approach, it seems reasonable to consider re-introduction of lamotrigine after initial rash using a very-low-dose-escalation regime in children with severe or disabling epilepsy that has not responded adequately to other drugs. Until more data is available, it is strongly recommended that lamotrigine should be stopped immediately if a rash attributable to the drug occurs and that re-introduction after initial rash should only be undertaken in centres capable of providing close supervision. Lamotrigine should probably not be re-introduced if the initial adverse effect was serious.

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